

WHAT IS CLAIMED IS:

1. A method of inducing differentiation of at least one epithelial cell comprising exogenously providing at least one source of at least one Notch agonist to at least one epithelial cell whereby the Notch pathway is activated within at least one epithelial cell such that differentiation of at least one epithelial cell is induced.
2. The method of claim 1, wherein at least one epithelial cell is a keratinocyte.
3. The method of claim 1, wherein at least one epithelial cell is a pre-malignant cell.
4. The method of claim 1, wherein at least one source of at least one Notch agonist is at least one constitutively active derivative of the Notch protein which is provided to the at least one epithelial cell intracellularly.
5. The method of claim 1, wherein at least one source of at least one Notch agonist is at least one antisense nucleotide targeting at least one endogenous inhibitor(s) or inhibiting pathway(s) that antagonizes and/or down-regulate(s) the Notch pathway, which is provided to the at least one epithelial cell intracellularly to attenuate the inhibition, and thereby activate, the Notch pathway within the at least one epithelial cell.
6. The method of claim 1, wherein at least one source of at least one Notch agonist is at least one ligand for at least one Notch protein, which is provided extracellularly to at least one epithelial cell.
7. The method of claim 6, wherein at least one Notch ligand is selected from the group of ligands consisting of Jagged 1, Jagged 2, Lunatic-Fringe, Manic-Fringe, Radical Fringe, Delta, Serrate, and active fragments and derivatives thereof.
8. The method of claim 6, wherein at least one Notch ligand is a protein having a sequence of amino acids consisting essentially of one of SEQ ID NOs: 2-12, active fragments, and derivatives thereof.
9. The method of claim 6, wherein at least one ligand is a Jagged 1 derivative derived from the Delta/Serrate/LAG-2 domain of hJagged 1.
10. The method of claim 6, wherein at least one ligand is provided to at least one epithelial cell in a composition comprising the Notch ligand and a physiologically-compatible carrier.
11. The method of claim 6, wherein at least one ligand is provided by inducing at least one second cell in the region of the epithelial cell to produce the ligand.

12. The method of claim 11, wherein at least one second cell is induced to produce the ligand by providing at least one chemical agent to the second cell to which the second cell responds by producing at least one Notch ligand.

13. The method of claim 11, wherein at least one expression cassette
5 encoding at least one Notch ligand is introduced into at least one second cell such that the second cell produces at least one Notch ligand.

14. The method of claim 1, wherein at least one epithelial cell is *in vivo*.

15. The method of claim 1, wherein at least one epithelial cell is *ex vivo*.

16. The method of claim 1, wherein at least one epithelial cell is within
10 cutaneous epithelial tissue or epidermal equivalent.

17. The method of claim 1, wherein at least one epithelial cell is within extracutaneous epithelium selected from the group of epithelial tissues consisting of oral mucosal, cornea, gastrointestinal epithelia, urogenital epithelia, and respiratory epithelia.

18. A method for inducing formation of at least one barrier within
15 epithelium comprising exogenously providing at least one source of at least one Notch agonist to at least one epithelial cell within the epithelium such that at least one epithelial cell is induced to form a barrier within the epithelium.

19. The method of claim 18, wherein the barrier is a stratum corneum.

20. The method of claim 18, wherein at least one source of at least one Notch agonist is at least one constitutively active derivative of the Notch protein which is provided to the at least one epithelial cell intracellularly.

21. The method of claim 18, wherein at least one source of at least one Notch agonist is at least one antisense nucleotide targeting at least one endogenous
25 inhibitor(s) or inhibiting pathway(s) that antagonizes and/or down-regulate(s) the Notch pathway, which is provided to the at least one epithelial cell intracellularly to attenuate the inhibition, and thereby activate, the Notch pathway within the at least one epithelial cell.

22. The method of claim 18, wherein at least one source of at least one Notch agonist is at least one ligand for at least one Notch protein, which is
30 provided extracellularly to at least one epithelial cell.

23. The method of claim 22, wherein at least one Notch ligand is selected from the group of ligands consisting of Jagged 1, Jagged 2, Lunatic-Fringe, Manic-Fringe, Radical Fringe, Delta, Serrate, and active fragments and
35 derivatives thereof.

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24. The method of claim 22, wherein at least one Notch ligand is a protein having a sequence of amino acids consisting essentially of one of SEQ ID NOs: 2-12, active fragments, and derivatives thereof.

25. The method of claim 22, wherein at least one ligand is a Jagged 1 derivative derived from the Delta/Serrate/LAG-2 domain of hJagged 1.

26. The method of claim 22, wherein at least one ligand is provided to at least one epithelial cell in a composition comprising the Notch ligand and a physiologically-compatible carrier.

27. The method of claim 22, wherein at least one ligand is provided by inducing at least one second cell in the region of the epithelial cell to produce the ligand.

28. The method of claim 27, wherein at least one second cell is induced to produce the ligand by providing at least one chemical agent to the second cell to which the second cell responds by producing at least one Notch ligand.

29. The method of claim 27, wherein at least one expression cassette encoding at least one Notch ligand is introduced into at least one second cell such that the second cell produces at least one Notch ligand.

30. The method of claim 18, wherein at least one epithelial cell is *in vivo*.

31. The method of claim 18, wherein at least one epithelial cell is *ex vivo*.

32. The method of claim 18, wherein at least one epithelial cell is within cutaneous epithelial tissue or epidermal equivalent.

33. The method of claim 18, wherein at least one epithelial cell is within extracutaneous epithelium selected from the group of epithelial tissues consisting of oral mucosal, cornea, gastrointestinal epithelia, urogenital epithelia, and respiratory epithelia.

34. A method for producing differentiated epidermis comprising culturing undifferentiated epidermal tissue in the presence of at least one source of a Notch agonist to the epidermal tissue whereby the Notch Pathway is activated within at least one cell of the epidermal tissue such that differentiation of the epidermis is induced.

35. The method of claim 34, wherein the epidermal tissue is cultured by being submerged in a solution comprising at least one source of a Notch agonist.

36. A method of assaying for genetic propensity of a patient to develop a disorder associated with epithelial barrier formation, the method comprising obtaining DNA or RNA from the patient, determining a characteristic of the DNA

or RNA from the patient that encodes at least one protein selected from Notch proteins and Notch ligands, and assessing whether characteristic differs from the corresponding wild-type characteristic.

- 5 37. The method of claim 36, wherein genomic DNA is obtained and sequenced.
38. The method of claim 36, wherein cDNA is obtained and sequenced.
39. The method of claim 36, wherein RNA is obtained and sequenced.
- 10 40. A protein having a sequence of amino acids consisting essentially of the amino acid sequence of one of SEQ ID NOs:9-12 or a conservative substituent thereof.
41. The protein of claim 40, wherein the protein is a Notch ligand.
42. A method of retarding the progression of a pre-malignant epithelial cell towards malignancy, comprising exogenously providing at least one source of at least one Notch agonist to a pre-malignant epithelial cell, whereby the
- 15 progression of the cell towards malignancy is retarded.
43. A method of retarding the progression of a skin cancer, comprising administering to skin cancerous cells an agonist or antagonist of the Notch pathway, whereby upon contact with the agonist or antagonist of the Notch pathway, the progression of the skin cancer is retarded.
- 20 44. The method of claim 43, wherein the skin cancer is selected from the group of skin cancers consisting of aggressive melanoma, aggressive cutaneous T-cell Lymphoma (CTCL), aggressive squamous cell carcinoma, and aggressive basal cell carcinoma and the method involves administering an antagonist of the Notch pathway.
- 25 45. The method of claim 43, wherein the cancer is aggressive melanoma.
46. The method of claim 43, wherein the cancer presents as aggressive CTCL that presents in the skin.
47. The method of claim 43, wherein the antagonist is a gamma
- 30 secretase inhibitor.
48. The method of claim 43, wherein the antagonist is a protein having a sequence of amino acids consisting essentially of the amino acid sequence of one of SEQ ID NOs:16 or 18 or a conservative substituent thereof.
- 35 49. The method of claim 43, wherein the skin cancer is selected from the group of skin cancers consisting of non-aggressive melanoma, non-aggressive cutaneous T-cell Lymphoma (CTCL), non-aggressive squamous cell carcinoma,

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and non-aggressive basal cell carcinoma and the method involves administering an agonist of the Notch pathway.

50. A method of diagnosing aggressive melanoma, comprising obtaining a tissue biopsy from a patient, assaying the tissue biopsy for the
- 5 overexpression of a protein selected from the group of proteins consisting of Notch ligands, Notch receptors, or endothelial cell markers/adhesion molecules, whereby the overexpression of one or more of the proteins leads to the positive diagnosis of aggressive melanoma within the patient.

51. The method of claim 50, wherein the tissue biopsy is assayed for
- 10 one or more proteins from the group of proteins consisting of JAG-1, JAG-2, and Delta, Notch-1, Notch-2, Notch-3, Notch-4, CD31, CD34, or CD54.

52. The method of claim 51, wherein the tissue biopsy is assayed for the overexpression of two or more of the proteins, and the overexpression of two or more of the proteins leads to the positive diagnosis of aggressive melanoma within
- 15 the patient

53. A method of diagnosing CTCL, comprising obtaining a tissue biopsy from a patient, assaying the tissue biopsy for the expression of a T-cell-specific marker and a Notch receptor in a first cell within the tissue biopsy, and for the expression of a Notch ligand in a second cell within the tissue sample, whereby
- 20 the staining pattern leads to the positive diagnosis of aggressive lymphoma within the patient

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